Amendments to Specification

Please delete the paragraph bridging lines 5-7 on page 11.

Please replace the paragraph bridging lines 8-10 on page 11 with the following revised paragraph:

Figure 2 shows MMP-8 S1' amino acid backbone residues which reside within 5 Å of a complexed inhibitor molecule.

Please delete the paragraph bridging lines 11-12 on page 11.

Please replace the paragraph bridging lines 13-16 on page 11 with the following revised paragraph:

Figures 3 and 4 show the effect of progressively lengthening the P1' group of an MMP inhibitor on the conformation of the substituents on amino acid residues of the S1' pocket.

Please delete the paragraphs bridging lines 17-23 on page 11.

Please replace the paragraph bridging lines 24-25 on page 11 with the following revised paragraph:

Figure 5 shows the (φ,ψ) distribution among the 25 amino acid residues of MMP-8 from 222 to 231.

Please delete the paragraph bridging lines 26-28 on page 11.

Please replace the paragraph bridging lines 6-19 on page 24 with the following revised paragraph:

The catalytic domain (residues 85-242) of MMP-8, neutrophil collagenase, folds into a compact globular structure. It has an approximate diameter of 30 Å. The inhibitors interact with the protein through chelation of the catalytic zinc ion, hydrogen bonding with the backbone -NH-

of Leu 160, and hydrophobic interactions in the nonpolar S1' pocket. In MMP-8, the S1' pocket is formed from residues 193-197 that form a turn of a longer helix and residues 214-229 of a loop region. The S1' pocket in MMP-8 is not as deep as in some other MMPs (e.g., stromelysin). The conformation of the S1' pocket changes as the P1' substituent on the inhibitor is made progressively longer.

Please replace the paragraph bridging pages 24 and 25 (*i.e.*, page 24, line 20 to page 25, line 8) with the following revised paragraph:

X-ray crystallographic techniques described herein showed the co-extensive reach of the P1' arms of the inhibitors XII, IX, X, and XI, except that as the alkyl group of the 4-alkylbenzamide moiety increases in length, the steric requirements of each inhibitor also increases. The P1' arm of each inhibitor fits into the MMP-8 S1' pocket. In order to accommodate an increase in the steric requirement of the P1' arm, the amino acid residues of the S1' pocket must change their conformations.

Please replace the paragraph bridging lines 9-16 on page 25 with the following revised paragraph:

Figure 2 shows MMP-8 S1' amino acid backbone residues which reside within 5 Å of a complexed inhibitor molecule as determined by the X-ray crystallographic techniques described herein. A blank in Figure 3 indicates that the residue lies within 5 Å of the inhibitor whereas the word "no" indicates that the residue lies further than 5 Å from the complexed inhibitor.

Please delete the paragraphs bridging lines 17-22 on page 25.

Please replace the paragraph bridging lines 23-34 on page 25 with the following revised paragraph:

X-ray crystallography of the complex of the compound of Formula XII or the compound of Formula XIV with MMP-8 showed that the P1' group (including the 4-propylbenzamide moiety) of compound XII sterically interferes with the side chain of the Arg 222 (R222) residue of the S1' pocket of MMP-8, while the P1' group of compound XIV is much shorter and does not

sterically interfere with the Arg 222 side chain. Complexed compound XII causes the Arg 222 side chain to move out of the way of the large P1' group of XII.

Please replace the paragraph bridging pages 25 and 26 (*i.e.*, page 25, line 35 to page 26, line 9) with the following revised paragraph:

Figure 3 shows a comparison of the X-ray crystallographic conformation of amino acid residues in the S1' pocket of MMP-8 when either the compound of Formula XII (black) or the compound of Formula IX (grey) is complexed with MMP-8. The P1' group of compound IX (including the 4-pentylbenzamide moiety) is larger still than the P1' group of compound XII. Because of increased steric interference, the P1' group of compound IX causes the side chain of the Arg 222 (R222) residue of the S1' pocket of MMP-8 to move even further away from the pocket than does the P1' group of compound XII.

Please replace the paragraph bridging lines 10-20 on page 26 with the following revised paragraph:

The P1' group of X (including the 4-hexylbenzamide moiety) is larger still than the P1' group of XII. X-ray crystallography showed that, due to increased steric interference, the P1' group of compound X causes the side chain of the Arg 222 (R222) residue of the S1' pocket of MMP-8 to move as far or further away from the pocket than does the XII P1' group.

Please replace the paragraph bridging lines 21-26 on page 26 with the following revised paragraph:

Figure 4 shows a comparison of the X-ray crystallographic conformation of amino acid residues in the S1' pocket of MMP-8 when either the compound of Formula XII (black) or the compound of Formula XI (grey) is complexed with MMP-8. This Figure shows a result similar to the comparison between compounds XII and X.

Please delete the paragraph bridging lines 27-30 on page 26.

Please replace the paragraph bridging pages 26 and 27 (*i.e.*, page 26, line 31 to page 27, line 6) with the following revised paragraph:

X-ray crystallography of the amino acid backbone of the S1' pocket of MMP-8 when either the compound of Formula XII or the compound of Formula XIV is complexed with MMP-8 showed that compound XII affects the conformation of the side chain of the Arg 222 (R222) residue of the Sl' pocket relative to compound XIV. It also showed that each compound has essentially no effect on the conformation of the amino acid backbone. Tyr 227 (Y227) shows little change when either compound XII or XIV is complexed in the S1' pocket.

Please replace the paragraph bridging lines 6-16 on page 27 with the following revised paragraph:

X-ray crystallography of the amino acid backbone of the S1' pocket of MMP-8 when either the compound of Formula XII or the compound of Formula X is complexed with MMP-8 showed that the longer 4-pentylbenzamide moiety of compound X causes the backbone to deform significantly relative to the case in which compound XII is complexed. In addition, compound X causes the Arg 222 and Tyr 227 side chains to move significantly relative to the case in which compound XII is complexed.

Please replace the paragraph bridging lines 17-26 on page 27 with the following revised paragraph:

X-ray crystallography of the amino acid backbone of the S1' pocket of MMP-8 when either the compound of Formula XII or the compound of Formula IX is complexed with MMP-8 showed that the longer 4-pentylbenzamide moiety of compound IX causes the backbone to deform significantly relative to the case in which compound XII is complexed. In addition, compound IX causes the Arg 222 and Tyr 227 side chains to move significantly relative to the case in which compound XII is complexed.

Please replace the paragraph bridging lines 27-36 on page 27 with the following revised paragraph:

X-ray crystallography of the amino acid backbone of the S1' pocket of MMP-8 when

either the compound of Formula XII or the compound of Formula XI is complexed with MMP-8 showed that the longer 4-hexylbenzamide moiety of compound XI causes the backbone to deform significantly relative to the case in which compound XII is complexed. In addition, XI causes the Arg 222 and Tyr 227 side chains to move significantly relative to the case in which XII is complexed.

Please replace the paragraph bridging lines 1-11 on page 28 with the following revised paragraph:

Complexes of MMP-8 with compounds XII and XIV show similar temperature factors indicating that the MMP-8 backbone has similar thermal motion in both cases. However, MMP-8 complexes with compounds XI, X, and IX cause a progressive increase in the temperature factor in residues 221-230, indicating that they are causing greater thermal motion in that region of the S1' pocket of MMP-8 relative to compounds X or XIV.

Please replace the paragraph bridging lines 12-13 on page 28 with the following revised paragraph:

Figure 5 shows the (φ,ψ) distribution among the amino acid residues of MMP-8 from 222 to 231.

Please replace the paragraph bridging lines 14-30 on page 28 with the following revised paragraph:

Comparison between the electrostatic surfaces of the MMP-8 complex with compounds XIV and XI showed that compound XI has caused a change in the conformation of MMP-8 relative to compound XIV as evidenced by the opening created by compound XI in the S1' pocket caused by the change in conformation of the amino acid residue backbone of MMP-8. This opening is absent from the compound XIV-MMP-8 complex. The electrostatic surfaces were calculated using the GRASP program (A. Nicholls et al., "Protein folding and association: Insights from the interfacial and thermodynamic properties of hydrocarbons," *Protein Str. Funct. Gen.* 11, 281-296 (1991)).

Please replace the paragraph bridging pages 28 and 29 (*i.e.*, page 28, line 31 to page 27, line 2) with the following revised paragraph:

Stepwise changes of the MMP-8 protein are observed in progressing from complexes of MMP-8 with XIV, XII, IX, X, and XI. The S1' pocket becomes deeper, first by the movement of amino acid residue side chains (especially Arg 222 and Tyr 227), then by a movement of the backbone in the 224-228 region.